Risk factors for developing cardiac toxicities in cancer patients treated with panitumumab combination therapy

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Abstract

Background Panitumumab, a novel anti-epidermal growth factor receptor (EGFR) monoclonal antibody (mAb), has been approved for the treatment of advanced colorectal cancer (CRC), and it is also being studied in other types of cancer. However, an increased risk of cardiac toxicities has been observed in some trials. The current study aims to evaluate the patterns and risk of cardiac toxicities by performing post hoc analyses of randomized controlled trials that evaluated treatment with or without panitumumab in advanced cancer patients. **Methods** Data were obtained from four randomized controlled trials (NCT00115765, NCT00339183, NCT00364013, and NCT00460265) which included a total of 3,243 patients with metastatic colorectal or head and neck carcinoma. The incidence of cardiac toxicity was assessed by simple incidence rates and rates per 100 person-years. Univariate and multivariate cox proportional hazards regression was conducted to investigate factors predicting the development of any cardiac event, cardiac arrhythmias and ischemic event. **Results** In comparison with controls, the use of panitumumab-containing therapy in cancer was associated with a significantly increased risk of developing cardiac arrhythmias (HR1.42, 95%CI: 1.02-1.96, $p=0.036$), but not for any cardiac event (HR1.16, 95%CI: 0.90-1.50, $p=0.24$) or ischemic event (HR 0.61, 95%CI: 0.35-1.07, $p=0.087$). The absolute rate of developing cardiac arrhythmia was 10.0 events per 100 person-years for those receiving combination therapy and 7.5 events per 100 person-years for those receiving chemotherapy alone. Within multivariate cox regression analysis for factors predicting any cardiac toxicity, pre-existing hypertension($p=0.0013$) or history of cardiac diseases ($p=0.01$) were predictive for occurrence of any cardiac toxicity. Additionally, development of cardiac arrhythmias was associated with a pre-existing hypertension ($p=0.033$), history of cardiac disease ($p=0.055$) or panitumumab usage ($p=0.046$) in multivariate regression analysis. **Conclusion** The addition of panitumumab to chemotherapy increases the risk of developing cardiac arrhythmia, but not for any cardiac toxicity or ischemic events. Patients with pre-existing hypertension or history of cardiac diseases are at high risk for developing cardiac toxicities when receiving panitumumab treatment.

Background

The EGFR is a transmembrane glycoprotein receptor belonging to the ErbB family of receptor tyrosine kinases (RTKs), which includes ErbB-1 (EGFR), ErbB-2 (HER2/neu), ErbB-3 (HER3), and ErbB-4 (HER4) [1, 2]. The EGFR signal pathway plays an important role in cell proliferation, differentiation, and migration by activating two major pathways (RAS/RAF/MAPK/ERK and PI3K/AKT/mTOR pathway) in solid tumors[3–5]. As a result, overactivation of EGFR signaling pathways is commonly detected in various malignant tumors, including non-small cell lung cancer (NSCLC), breast cancer[6], head and neck cancer[7], and colorectal cancer[8, 9]. To attenuate the effects that EGFR pathways take on cancers, molecular agents specially targeting EGFR have been widely investigated in order to inhibit its activity. Currently, two classes of EGFR-targeted agents, including anti-EGFR monoclonal antibodies (mAbs) and the small molecular tyrosine kinase inhibitors(TKIs), has been shown to improve cancer patients survival,

and anti-EGFR agents have been well-established therapeutic agents incorporated into standard care for several solid tumors[10–12]. Therefore, the usage of these drugs could be increased in the near future.

Panitumumab, a fully humanized monoclonal antibody (mAb) targeting epidermal growth factor receptor (EGFR) antibody, has been approved for use monotherapy or in combination with chemotherapy for RAS wide type metastatic colorectal cancer (mCRC)[13, 14]. In comparison with traditional chemotherapy agents, panitumumab is generally well tolerated in many patients, and do not usually produce systemic toxicities such as nausea, vomiting, diarrhea, alopecia, and bone marrow suppression. However, several previous study have found that the use of anti-EGFR mAb could increase the risk of developing specific toxicities, such as infection[15, 16], thrombosis[17] and skin rash[18]. Cardiac toxicity is a rare but serious adverse event with novel molecular targeted agents[19–21]. Several previous studies have found that the use of angiogenesis inhibitors, such as bevacizumab[22, 23] and sorafenib[24, 25], significantly increased the risk of developing cardiac toxicities. Cardiac toxicity associated with panitumumab has been reported in clinical trial. However, the sample size of these studies are generally small and the clinical information could not be collected. Therefore, no study has comprehensively and prospectively analyzed the risk factors related to the development of cardiac toxicity in cancer patients, who have been administered with panitumumab. As a result, weperform the present study toinvestigate the overall incidence and risk factors for developing cardiac toxicity in cancer patients underwent panitumumab-containing therapy by performing post hoc analyses four prospective clinical trials.

Materials And Methods

This study protocol was approved by the institutional review board at the ethics committee of Rui Jin Hospital affiliated medicine school of Shanghai Jiao Tong University before initiation and don't need ethical standard statement.

About PDS and study cohorts

Project Data Sphere (PDS) is an independent, not-for-profit data-sharing platform, which provides one place where the research community could voluntarily share, integrate, and analyze historical, patient-level data from prospective clinical trial in order to advance future cancer research[26]. The present analysis is based on a pooled analysis of individual patient data from four phase III trials evaluating combination of panitumumab with chemotherapy versus chemotherapy alone for advanced cancer patients(NCT00115765, NCT00339183, NCT00364013, and NCT00460265)[7, 13, 27, 28]. The primary results of these trials were analyzed and published previously. Supplemental Table 1 summarized details of each of these trials. Informed consent was obtained from all included participants in all included studies. Both experimental and active comparator arm datasets were available in the PDS platform for the included trials. Overall, a total of 3,243 patients were available from the combined dataset. Three of the included trials investigate the efficacy of panitumumab in advanced colorectal cancer, and the remaining one trial in head and neck cancer patients(supplemental table 1).

Data collection:

The available data of the phase III trial contains data about age at diagnosis, race, gender (male or female), geographic region, primary tumor site, Eastern Cooperative Oncology Group (ECOG) performance score, pre-existing diabetes, pre-existing hypertension, history of cardiac disease, cumulative dose of panitumumab, body mass index (BMI) and treatment regimens. Moreover, incidence and grade of cardiac toxicities were also collected. In addition, specific cardiac arrhythmias and ischemic events were also collected. Cardiac toxicities were graded according to common terminology criteria of adverse events.

According to the available clinical trial protocol, all included patients should have adequate organ function (including liver, renal and bone marrow functions) as well as acceptable performance status. Patients were excluded from the trials if they had Clinically significant cardiovascular disease (including myocardial infarction, unstable angina, symptomatic congestive heart failure, serious uncontrolled cardiac arrhythmia) 1 year prior to randomization. Patients with a cardiac event were identified from study databases by one of the following adverse events: cardiac arrest, ischaemic coronary artery disease, palpitations, tachycardia, congestive heart failure, cardiac conduction disorders, supraventricular arrhythmias—atrial fibrillation, sinus tachycardia, bradycardia, ventricular arrhythmia, Left Ventricular Ejection Fractions (LVEF) decrease, myocardial infarction, and myocardial ischemia.

Statistical consideration

Simple descriptive statistics were conducted (including frequencies and percentages) to determine the baseline characteristics and the overall incidence of any cardiac event, cardiac arrhythmia, and ischemic event. The time to first cardiac event analysis was performed by Kaplan-Meier method. To adjust for different durations of follow-up, first cardiac event rates per 100 person-years were computed as previously described. Poisson regression was used to compare rates per 100 person-years as a ratio between panitumumab-treated patients and control patients. The number of person-years of observation was defined as the sum of the times from the start of treatment to the first cardiac event for patients with an event; for patients without a cardiac event, the observation time was defined as the start of treatment to the last date of treatment plus 30 days. First date of treatment was defined as the date when the first panitumumab or control treatment was administered.

In order to evaluate factors predicting the risk of developing cardiac toxicities, univariate cox proportional hazards regression analysis of the time to the first cardiac event was used to calculate hazard ratios (HRs); Factors with $p < 0.05$ in the univariate analysis were then included in the multivariate logistic regression analysis. In particular, the cutoff point of cumulative panitumumab dosage affecting cardiac event was determined by receiver operating characteristic (ROC) curve. A two-tailed P-value < 0.05 was considered statistically significant. Statistical analyses were conducted through SPSS statistical software (IBM;NY) version 20.0.

Results

Patients characteristics

Baseline characteristics of the included 3,243 patients were shown in Table 1. A total of 1620 patients received panitumumab-containing therapy, and 1623 patients were randomly assigned to controlled groups. Among the 3243 patients, 851 (26.2%) had colon cancer, 1872 (57.8%) had rectum cancer, and 520 (16.0%) had head and neck cancer. Mean age was 60.47 year (SD: 10.51 years). Mean cumulative dosage of panitumumab were 2111.75mg (SD: 3703.22 mg). Male patients comprised 64.6% of all included patients. 92.7% of the patients were Caucasian race, and 49.8% of the patients had ECOG score of 0. 20.7% of the patients with baseline hypertension, and 5.9% patients had diabetes (table 1).

Details of cardiac toxicities

A total of 246 patients developed any cardiac event (12.4%). Among which, 152 developed cardiac arrhythmia, 50 patients developed ischemic attack and the remaining 44 patients developed other types of cardiac toxicities. Cardiac arrhythmia were regarded as grade 1 in 75 patients, grade 2 in 40 patients, grade 3 in 19 patients, grade 4 in 7 patients and grade 5 in 11 patients. And ischemic attacks were regarded as grade 1 in 14 patients, grade 2 in 11 patients, grade 3 in 13 patients, grade 4 in 7 patients and grade 5 in 5 patients.

Overall incidence of cardiac toxicities

Treatment with panitumumab-containing therapy, compared with controlled treatment, increased the overall incidence of any cardiac event from 6.8% (chemotherapy alone)

to 8.4% (panitumumab combination treatment), which is a difference of 1.6% (95% CI: 0.3% to 3.5%), and increased the absolute rate per 100 person-years of exposure from 14.9 to 13.5 events (ratio = 1.10, 95%CI = 0.85–1.43; $p = 0.46$), although the difference was not statistically significant (Table 2). The two-year any cardiac event free survival was 81% in panitumumab group versus 83% in controls. In a Kaplan-Meier analysis of the time-to-first cardiac event for patients in the pooled population, panitumumab-treated patients had a tendency to increase the incidence of any cardiac event than control patients (HR for any cardiac event = 1.16, 95% CI: 0.90–1.50; $p = 0.24$) (figure 1A). Then we investigated the incidence difference of specific cardiotoxicity between the two groups. As for cardiac arrhythmia, the absolute rate per 100 person-years was increased from 3.7% (chemotherapy alone) to 10.0% (panitumumab-containing regimen). The two-year cardiac arrhythmias free survival was 87% in panitumumab group versus 93% in controls. Kaplan-Meier analysis showed that the use of panitumumab significantly increased the risk of developing first cardiac arrhythmia when compared to controls (HR 1.42, 95%CI: 1.02–1.96, $p = 0.036$, Figure 1B). As for ischemic event, no increased rate per 100 person-years was observed between the groups (2.1 events per 100 person-years versus 3.7 events per 100 person-years, figure 1C). In addition, no

significant difference of other types of cardiac toxicities was observed between the two groups (HR 1.24, 95%CI: 0.68–2.25, $p = 0.48$, figure 1D).

Predictors for developing of cardiac toxicity

The following factors were investigated in univariate Cox regression analysis as potential risk factors for developing any cardiac toxicity: age at diagnosis, gender, race, ECOG score, tumor location, BMI, diabetes mellitus, pre-existing hypertension, history of cardiac disease, treatment regimen, and cumulative dosage of panitumumab. The results of cutoff point determination for cumulative dose of panitumumab indicated that 7240mg was the optimal point, which was supported by ROC curve. The results of univariate and multivariate Cox regression analyses for any cardiac toxicity were shown in Table 3. Univariate and multivariate cox analysis for risk factors associated with any cardiac toxicity were pre-existing hypertension (HR 1.75, 95%CI: 1.24–2.46, $p = 0.0013$), and history of cardiac disease (HR 1.67, 95%CI: 1.23–2.47, $p = 0.01$), respectively.

A similar set of factors were assessed in cox regression analysis as predictors for cardiac arrhythmias (table 4). Univariate and multivariate analysis showed that pre-existing hypertension (HR 1.62, 95%CI: 1.04–2.55, $p = 0.033$) and panitumumab-containing therapy (HR 1.59, 95%CI: 1.01–2.53, $p = 0.046$) were associated with risk for developing cardiac arrhythmias. Likewise, the same set of factors were investigated for predictors of ischemic event. No significant predictors for developing ischemic events were found (table 5).

Discussion

Molecular inhibition of EGFR pathway is a promising anticancer strategy and monoclonal antibodies to EGFR are undergoing extensive evaluation in preclinical and clinical trials[29–31]. Panitumumab, a humanized anti-EGFR mAb, have been approved as a single-agent for the treatment of EGFR-expressing mCRC with k-ras wild-type status after disease progression to oxaliplatin- and irinotecan-based standard therapy[27, 28]. Concern has arisen regarding the risk of cardiac toxicity with the administration of anti-EGFR mAb, including panitumumab[32]. However, the absolute hazards ratios of these factors haven't been clearly determined. Therefore, we perform the current analysis to comprehensively evaluates the risk factors associated with cardiac toxicity in cancer patients treated with panitumumab-containing treatment based on individual patient data of three prospective well-controlled clinical trials.

To our best knowledge, this is the largest comprehensive study to investigate the patterns and risk predictors for cardiac toxicity among cancer patients receiving panitumumab-containing regimen. The pooled results shows a modest increase in the risk of cardiac arrhythmia among cancer patients treated with panitumumab, but not for any cardiac event or ischemic event. As for cardiac arrhythmia, the absolute rate per 100 person-years has been increased from 3.7% (chemotherapy alone) to 10.0% (panitumumab-contain regimen). We also identified clinical characteristics that may be associated with an increase in this risk. Pre-existing hypertension (HR 1.62, 95%CI: 1.04–2.55, $p = 0.033$) and

panitumumab-containing therapy (HR 1.59, 95%CI: 1.01–2.53, $p = 0.046$) were independent risk factors for developing cardiac arrhythmias, while pre-existing hypertension (HR 1.75, 95%CI: 1.24–2.46, $p = 0.0013$) and history of cardiac disease (HR 1.67, 95%CI: 1.23–2.47, $p = 0.01$) are independently risk factors for developing any cardiac toxicity.

Preventing drug-related cardiac toxicity remains an important challenge in oncology. The clinical spectrum of cardiac dysfunction is associated with antineoplastic agents, but also related with the dose and treatment schedule, patients age and presence of co-existing cardiac disease. In the present study, we find that pre-existing hypertension and/or history of cardiac diseases, but not for patient age and drug dosage, are independent risk factors for developing cardiac toxicity in cancer patients receiving panitumumab. Therefore, recognizing these two factors would help physicians prevent cardiac toxicity by risk modification and/or careful monitoring during therapy.

Cardiac toxicity is a rare but significant complication associated with anti-EGFR mAb, which ranges from subclinical abnormalities to being life-threatening and sometimes fatal events[32]. Currently, the detailed mechanism of anti-EGFR mAb-related cardiac arrhythmias remains unclear. Pre-clinical research showed that EGFR family and some of its ligands plays an important role in myocardial cell physiology and development[33]. For example, ERBB4 is the predominant neuregulin 1 receptor in postnatal rat ventricular muscle, and its expression in adult animals is limited to cardiac myocytes[34, 35]. Additionally, anti-EGFR mAb was associated with a decrease in angiogenic factors and number of micro-vessels, while angiogenesis inhibition could cause potential cardiovascular toxicity[36]. Another possible explanation for cardiac toxicity is that the use of anti-EGFR mAb could lead to electrolyte imbalance[37, 38]. For example, it has been reported that the use of panitumumab is associated with an increased risk of developing hypomagnesemia, while hypomagnesemia can lead to cardiovascular (arrhythmias, hypertension, cardiomyopathy) complications[37, 39]. Hypocalcemia and hypokalemia have also been consistently reported across clinical trials[40–42]. However, further studies are still needed to investigate the detailed mechanism of cardiac toxicities associated with anti-EGFR mAb.

There are several limitations needed to be concerned. First of all, the raw incidence rates in these analyses may overestimate the risk of a cardiac event due to the delayed time to progression and corresponding longer safety observation duration in the panitumumab-treatment group, when compared to controlled treatment, although we used the Kaplan-Meier hazard estimates and the rate of events per 100 person-years to partially correct this observation difference. Secondly, patients received different cytotoxic agents combined with panitumumab, the impact of chemotherapy regimens on the risk of cardiac toxicity remains undetermined. Thirdly, the primary endpoint of the included studies are aimed to investigate the survival benefit of adding panitumumab in cancer patients, but not risk factors associated with cardiac toxicity. Thus, in spite of the randomized, prospective nature of the included studies, the present study provides a retrospective analysis of the pooled dataset of these included studies. Therefore, the finding of present study might be confounded by this pattern of study design.

Conclusion

The addition of panitumumab to chemotherapy increases the risk of developing cardiac arrhythmia, but not for any cardiac toxicity or ischemic events. Patients with pre-existing hypertension or history of cardiac diseases are at high risk for developing cardiac toxicities when receiving panitumumab treatment. Further prospective trials investigating the cardiac toxicities of panitumumab remains needed to confirm our findings.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.*Availability of data and material*

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Competing interests

The authors declare that they have no competing interests.*Funding*

None *Authors' contributions*

Conceived and designed the experiments: S. G. Z. Analyzed the data: WXQ and JYC. Contributed reagents/materials/analysis SGZ and WXQ. Wrote the manuscript: WXQ and JYC. All authors have read and approved the final manuscript.

EGFR, epidermal growth factor receptor; RTKs, receptor tyrosine kinases; NSCLC, non-small cell lung cancer; mAb, monoclonal antibody; mCRC, metastatic colorectal cancer; PDS, Project Data Sphere; ECOG, Eastern Cooperative Oncology Group; BMI, body mass index; HRs, hazard ratios; ROC, receiver operating characteristic;

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Tables

Table 1. baseline characteristics of included patients in the cohort (n=3243 patients):

Parameter	Number (%)
Age	
Mean(SD), year	60.47 (10.51)
Missing	0
Gender	
Male	2095 (64.6%)
Female	1148 (35.4%)
Race	
Caucasian	3005 (92.7%)
Others	236 (7.2%)
Missing	2 (0.1%)
Body mass index	
Mean (SD)	25.91 (5.21)
Missing	2 (0.1%)
ECOG	
0	1616 (49.8%)
1	1521 (46.9%)
2	106 (3.3%)
Missing	0
Primary tumor site	
Colon	851 (26.2%)
Rectum	1872 (57.8%)
Head and neck	520 (16.0%)
Unknown	0
Cumulative panitumumab dose	
Mean (SD), mg	2111.75 (3703.22)
Unreceived patients	1814 (55.9%)
Diabetes	
Yes	191(5.9%)
No	1597 (49.2%)
Unknown	1456 (44.9%)
Hypertension	
Yes	673 (20.7%)
No	1115 (34.4%)
Unknown	1456 (44.9%)
History of cardiac disease	
Yes	273 (8.4%)
No	1515 (46.7%)
Unknown	1456 (44.9%)
Any cardiac toxicity	
Yes	246 (12.4%)
No	2997 (87.6%)
Cardiac arrhythmia	
Yes	152 (4.7%)
No	3091 (95.3%)
Ischemic attacks	
Yes	50(1.5%)
No	3193 (98.5%)

Table 2 incidence of cardiac toxicity in the pooled population by treatment and type of cardiac events

	Panitumumab-treated patients (1620)	Controlled patients (1623)	<i>P</i> value
Incidence, No. (%)	136 (8.4%)	110 (6.8%)	
Rate in incidence	1.6% (0.3-3.5%)		
Person-years	913.8	812.3	
Rate per 100 py (95%CI)	14.9 (12.5-17.6)	13.5(11.1-16.3)	0.46
Rate per 100 py	1.10(0.85-1.43)		
Rate per 100 py	1.16(0.90-1.50)		0.24
Incidence, No. (%)	91 (5.5%)	61 (3.7%)	
Rate per 100 py	10.0 (8.0-12.2)	7.5(5.7-9.6)	
Rate per 100 py	1.42 (1.02-1.96)		0.036
Incidence, No. (%)	20 (1.1%)	30 (1.9%)	
Rate per 100 py	2.1(1.3-3.4)	3.7(2.5-5.3)	
Rate per 100 py	0.61(0.35-1.07)		0.087
Incidence, No. (%)	25 (1.8%)	19 (1.2%)	
Rate per 100 py	2.7(1.8-4.0)	2.3(1.4-3.7)	
Rate per 100 py	1.24(0.68-2.25)		0.48

Abbreviation: py, person-year;

Table 3 univariate and multivariate cox proportional hazards regression analysis of potential risk factors for any cardiac event

	Univariate			Multivariate		
	HR	95%CI	<i>p</i>	HR	95%CI	<i>p</i>
	1	-	-	-	-	-
	1.05	0.80-1.36	0.74	-	-	-
's	1	-	-	1	-	-
75 years	1.16	0.88-1.53	0.30	1.00	0.70-1.46	0.96
	1.66	1.10-2.49	0.015	1.28	0.81-2.02	0.14
n	1	-	-	1	-	-
	1.59	1.07-2.37	0.023	1.19	0.72-1.98	0.49
ce status	1	-	-	1	-	-
	1.43	1.11-1.85	0.0059	1.13	0.81-1.57	0.47
	1.88	0.98-3.59	0.056	0.95	0.30-3.02	0.93
ation	1	-	-	-	-	-
	1.06	0.79-1.42	0.72	-	-	-
l neck	1.29	0.86-1.95	0.21	-	-	-
nuous)	1.01	(0.99-1.04)	0.37	-	-	-
ellitus	1	-	-	1	-	-
	1.67	1.08-2.60	0.021	1.28	0.81-2.02	0.29
g hypertension	1	-	-	1	-	-
	1.95	1.41-2.70	0.001	1.75	1.24-2.46	0.0013
cardiac disease	1	-	-	1	-	-
	1.91	1.30-2.79	<0.001	1.67	1.23-2.47	0.01
lab-containing						

	1	-	-	-	-	-
		1.16 (0.90- 1.50)	0.24	-	-	-
≥ dose of gabapentin	1			-		
		1.21(0.94- 1.55)	0.14	-	-	-

Table 4 Univariate and multivariate cox proportional hazards regression analysis of potential risk factors for cardiac arrhythmias

	Univariate			Multivariate		
	HR	95%CI	p	HR	95%CI	p
	1	-	-	-	-	-
	1.14	0.81-1.60	0.46	-	-	-
Age	1	-	-	-	-	-
≥ 75 years	1.14	0.80-1.62	0.45	-	-	-
	1.31	0.74-2.32	0.34	-	-	-
Sex	1	-	-	-	-	-
Female	1.32	0.76-2.29	0.32	-	-	-
Marital status	1	-	-	-	-	-
Married	1.43	1.03-1.99	0.76	-	-	-
	1.84	0.80-4.25	0.08	-	-	-
Education	1	-	-	-	-	-
High school or less	0.94	0.64-1.38	0.72	-	-	-
Diabetes mellitus	1.54	0.95-2.51	0.21	-	-	-
	1.01	(0.98-1.05)	0.38	-	-	-
Smoking	1	-	-	-	-	-
Smoking hypertension	1.57	0.85-2.90	0.15	-	-	-
Cardiovascular disease	1	-	-	1	-	-
	1.66	1.06-2.59	0.027	1.62	1.04-2.55	0.033
Medication	1	-	-	1	-	-
Medication-containing regimen	1.85	1.09-3.14	0.022	1.68	0.99-2.86	0.055
Medication dose of	1	-	-	1	-	-
Medication		1.42 (1.02-1.96)	0.036	1.59	1.01-2.53	0.046
Medication	1	-	-	-	-	-
		0.84 (0.49-1.40)	0.49	-	-	-

Table 5 univariate and multivariate cox proportional hazards regression analysis of potential risk factors for ischemic attack

	Univariate			Multivariate		
	HR	95%CI	<i>p</i>	HR	95%CI	<i>p</i>
	1	-	-	-	-	-
	0.67	0.36-1.20	0.18	-	-	-
Age	1	-	-	-	-	-
≥ 75 years	1.19	0.62-2.30	0.60	-	-	-
	1.65	0.63-4.32	0.30	-	-	-
Sex	1	-	-	-	-	-
Male	2.03	0.86-4.80	0.11	-	-	-
Marital status	1	-	-	-	-	-
Married	1.99	1.07-3.72	0.03	-	-	-
	2.54	0.58-11.08	0.21	-	-	-
Education	1	-	-	-	-	-
High school or above	0.95	0.48-1.90	0.89	-	-	-
High school	1.23	0.48-3.15	0.66	-	-	-
Below high school	1.00	(0.95-1.06)	0.97	-	-	-
Diabetes mellitus	1	-	-	-	-	-
With	1.73	0.66-4.54	0.26	-	-	-
Without	1	-	-	-	-	-
Without	1.62	0.78-3.35	0.20	-	-	-
Cardiac disease	1	-	-	-	-	-
With	1.56	0.64-3.84	0.33	-	-	-
Without	1	-	-	-	-	-
Without		1.24 (0.68-2.25)	0.48	-	-	-
≥ 2 dose of panitumumab						
Yes						
No	1	-	-	-	-	-
	1.99	(0.94-4.22)	0.07	-	-	-

Figures

Figure 1

Kaplan-Meier analysis of time-to-first cardiac event for patients in the pooled population according to panitumumab treatment: (A) time-to-first any cardiac event; (B) time-to-first cardiac arrhythmia; (C) time-to-first cardiac ischemic event; (D) time-to-first other cardiac event

Supplementary Files

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